II. Support f r the Claims

Support for the present claims can be found throughout the specification as filed and the original claims.

All pending claims except claims 73 and 74 now recite the encoded P-TEFb subunits directly, without reference to being "substantially full length".

Except claims 73 and 74, all claims that refer to nucleic acid hybridization now do so without reference to "stringent hybridization conditions".

Support for the current "specifically" hybridizing language is present throughout the specification as filed. Particular written description support exists, for example, at least at page 69, lines 9-10 and 19-21 and at page 76, lines 11-14.

Independent claims 1 and 23 have been clarified as outlined above. The language of claim 23 now also better corresponds to that of claim 1.

Minor changes to improve the clarity of the language and/or to change the claim dependency are also included within claims 3, 4, 5, 7, 11 and 17.

Claims 15 and 31 are being revised to more succinctly refer to the "said" P-TEFb subunit of the preceding claim, rather than attempting to repeat the structural definition of the subunits.

The alternative embodiment originally recited within claim 18 is now represented in new claim 41.

Claim 19 has been revised to even further improve the clarity of the "fusion protein" terminology.

Most of the new dependent claims simply supply intermediate numbers of sequence continuity from the specification, and examination of such claims should not prove burdensome.

Applicant's representative has found that such intermediate claims are best added after any Restriction Requirement, in order to reduce excess claim fees for non-elected inventions.

Support for claims 33-40 is present in the original specification at least at page 16, line 25 to page 17, line 4 and at page 19, lines 1-12.

Claim 41 is supported by original claim 18.

In addition to the original claims, new claims 42-51 are supported by the specification at least at page 12, lines 10-14 and at page 13, lines 1-24.

New claims 52-64 are also supported by the original claims and by the specification at least at page 16, line 25 to page 17, line 4 and at page 19, lines 1-27.

Claim 65 is supported by the specification at least at page 26, line 2.

The new recombinant host cell claim, claim 66, is supported by the specification at least at page 20, line 23.

Each of claims 67-72 are independent claims directed to the subject matter of various earlier dependent claims, and are fully supported by the original claims and specification, as exemplified by the sections outlined above.

Claims 73 and 74 are modeled on the previous language of claims 1 and 23.

It will therefore be understood that no new matter is included within any of the pending claims.

III. Summary of Issues

Although various rejections have been entered, Applicant appreciates the Examiner's findings that the claimed invention has utility and is novel and non-obvious. Also, most claims are

noted to be free from rejection under 35 U.S.C. § 112, first paragraph, and are therefore supported by an enabling specification.

The present response fully addresses the Examiner's concerns and is believed to overcome all rejections. Should Examiner Tung identify any remaining issues, Applicant encourages the Examiner to telephone the undersigned representative so that any remaining concerns can be allayed in a timely and cost-effective manner.

IV. Rejection of Claims 1-32 Under 35 U.S.C. § 112, Second Paragraph

The Action first rejects claims 1-32 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite and for failing to particularly point out and distinctly claim the subject matter of the invention. Although Applicant respectfully traverses, the present claims have been clarified to address the Examiner's concerns.

A. Substantially Full Length

The Action first takes the position that the term "substantially full length" is a relative term that renders the claims indefinite (Action at page 2, Item 4). Applicant respectfully traverses. Both "relative terms" themselves and claim language including "substantially" are perfectly acceptable under the law.

The Federal Circuit and its predecessor court have repeatedly held that use of the term "substantially" does not, in itself, render a claim indefinite. In *In re Mattison*, 184 USPQ 484 (C.C.P.A. 1975), the terminology "to substantially increase the efficiency of the compound as a copper extractant" was found to be definite in view of the general guidelines contained in the specification. In *Andrew Corp. v. Gabriel Electronics*, 6 USPQ2d 2010 (Fed. Cir. 1988), the language "produces substantially equal E and H plane illumination patterns" was also found to be

definite - - because one of ordinary skill in the art would know what was meant by "substantially equal".

In this case, the Action contends that "the specification does not provide a standard for ascertaining the requisite degree [of substantially full length]" (Action at page 2, Item 4). In contrast, Applicant points out that the specification contains significant teaching on what constitutes a "substantially full length" P-TEFb subunit. For example, beginning at page 8, line 27, the specification explains:

> "The term 'substantially full length' as used herein, means that the genes and coding regions of the invention encode a substantially full length P-TEFb kinase or large subunit protein or polypeptide such that the subunit produced on expression of the gene or coding region includes each of the polypeptide regions or domains necessary to impart functional activity to the expressed product."

The specification then continues for numerous pages with further standards for ascertaining whether a sequence is a "substantially full length" sequence and whether a subunit has "functional activity". One of ordinary skill in the art would thus understand the meaning of the term "substantially" as it used in the present claims.

Nonetheless, and entirely without acquiescence, it will be noted that all but two of the pending claims have been clarified to remove the complained of language.

B. Fusion Protein

The Action at page 3, Item 6, next rejects claim 19 by questioning the antecedent basis for the term "said DNA segment encoding a P-TEFb subunit fusion protein".

Applicant respectfully points out that "said" applies to the term "DNA segment", which has proper antecedent basis in claim 1, from which claim 19 depends. The new language "fusion protein" is preceded by the term "a", which does not require antecedent basis in an earlier claim.

Nonetheless, Applicant has endeavored to further clarify claim 19 by more precisely defining the relationship between the recited elements. Those of ordinary skill in the art, being familiar with fusion protein technology, will clearly understand the claim as written.

C. Stringent Hybridization

Last under this section, the Action rejects the claims on the grounds that the term "stringent hybridization conditions" is allegedly indefinite. Applicant respectfully traverses.

The Action first takes the position that the term "stringent hybridization conditions" is not defined by the claim (Action at page 3, Item 7). The Federal Circuit has repeatedly held that the claims need not contain every definition of the invention, which should be reserved for the specification. "A claim need not 'describe' the invention, such description being the role of the disclosure". *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ 2d 1081, 1088 (Fed. Cir. 1986).

The Action next states that "the specification does not provide a standard for ascertaining the requisite degree [of stringent hybridization conditions]" (Action at page 3, Item 7). Applicant first points out that the specification is not required to set forth operating conditions necessary to achieve a desired result where such conditions would be routinely understood in the art. *In re Karnofsky*, 156 USPQ 682 (C.C.P.A. 1968); *In re Stephens*, 188 USPQ 659 (C.C.P.A. 1976). As nucleic acid hybridization is now a routine technical skill that is frequently practiced in the art, the specification could be silent on this issue and the claims would still be definite.

Nonetheless, it appears that the Action has overlooked the incredibly detailed teaching that the specification contains on hybridization technology and stringent hybridization. For example, in addition to the description of the P-TEFb DNA segments at pages 58-67, the

specification contains an entire section (pages 67-78) devoted to nucleic acid detection and hybridization embodiments. Moreover, Examples 4 and 5, which describe the cloning of P-TEFb subunits, demonstrate the successful execution of hybridization studies, including Northern blotting (page 170, second full paragraph; page 173, second full paragraph; page 180, sub-heading 4; see also, page 203, heading A).

In summary, the proper test of definiteness is whether, in the light of the teachings of the prior art and of the particular application disclosure, the claims set out and circumscribe, for one possessing an ordinary level of skill in the pertinent art, a particular area with a reasonable degree of particularity. *In re Moore*, 169 USPQ 236 (C.C.P.A. 1971). In light of the level of understanding in the art, and the detailed teaching in the specification, the original claims were sufficiently definite under 35 U.S.C. § 112, second paragraph.

In any event, and without acquiescing with the rejection in any way, all but two of the pending claims have been clarified to remove the complained of "stringent hybridization" language, thus addressing the stated concerns.

The § 112, second paragraph rejections as a whole are thus overcome and should be withdrawn.

V. Rejection of Claims 1, 4-6 and 23 under 35 U.S.C. § 112, First Paragraph

Claims 1, 4-6 and 23 are next rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being supported by an enabling specification. Applicant respectfully traverses.

Although Applicant contests the rejection as applied to claims 1, 4-6 and 23, the indication of subject matter already agreed to be fully enabled is appreciated. In fact, the

indication that each of claims 2, 3, 7-22 and 24-32 are fully enabled compels a finding of adequate enabling support for certain of the rejected claims.

The isolated coding regions of claim 11, defined as isolated coding regions that [specifically] hybridize to the nucleotide sequence of SEQ ID NO:3, SEQ ID NO:43 or SEQ ID NO:48 under stringent hybridization conditions, are fully enabled. Although the Action had concerns regarding the clarity of the "stringent" language, which are fully addressed herein, it is already agreed that one of ordinary skill in the art can make and use coding regions that hybridize to the nucleotide sequence of SEQ ID NO:3, SEQ ID NO:43 or SEQ ID NO:48 without undue experimentation.

Therefore, rejected claim 5, which recites "and wherein said coding region [specifically] hybridizes to the nucleotide sequence of SEQ ID NO:3, SEQ ID NO:43 or SEQ ID NO:48" must be enabled. The degree of contiguous sequence identity in the encoded product defined by claim 5 is irrelevant, as it has already been established that hybridizing coding regions are enabled.

Claims 15, 19, 20-22, 23-26 and 27-32 are all also free from rejection under § 112, first paragraph, and strongly support a finding of sufficient enablement for the rejected claims. Claim 15, in particular, supports rejected claim 23, as these claims both concern DNA segments with first and second coding regions that encode (or encode and express) the P-TEFb kinase and large subunits, respectively.

The rejection of claims 1, 4-6 and 23 rests on the allegation that the specification does not reasonably enable DNA segments that encode P-TEFb subunits that have at least about 7 contiguous amino acids in common with the recited SEQ ID NOs (Action bridging pages 3 and 4). Claim 5 should be immune from this ground of rejection as enabling support is imparted by

the requirement that the claimed DNA segments hybridize to the recited SEQ ID NOs, already found to be enabled in claim 11. The rejection as applied against claims 1, 4, 6 and 23 is also improper, as set forth below.

The essence of this rejection lies in the statement that "no guidance is provided on how to obtain or identify a P-TEFb based only upon at least 7 contiguous amino acids" (Action at middle of page 4), and the requirements for guidance on "enzymatically important" amino acids and working examples on "enzymatically active" large subunits (Action at bottom of page 4). These apparent standards for patentability (and the underlying assessment of enabling support) include various fundamental flaws, which are addressed in the following sections.

A. P-TEFb Definition

The Action's focus on the "7 contiguous amino acids" overlooks the fundamental requirement of the claim: that the encoded product be a "P-TEFb subunit". The sequence recitations are present in the claims to add supplementary structural features for further definition of the claimed invention. The sequence information is not to be interpreted in a vacuum, but read in light of the specification. *Slimfold Mfg. Co. vs. Kinkead Industries, Inc.*, 1 USPQ 2d 1563 (Fed. Cir. 1987). Therefore, the claims simply cannot be interpreted without reference to the requirement that an encoded product be a P-TEFb subunit.

The specification includes over 200 pages of detailed guidance on what constitutes a "P-TEFb subunit". In addition to the primary sequence information, the detailed guidance includes substantial information on molecular weight; sequence motifs; interaction with the counterpart (large and small, kinase and cyclin) subunit; interaction with viral proteins; and enzymatic activity, where desired (see sections **V(C)** and **V(D)**, below).

In light of such details, one of ordinary skill in the art would clearly be able to make and use a DNA segment that encodes a P-TEFb subunit without undue experimentation. The present rejection should be overcome on this basis alone. The specification "*must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements". *In re Marzocchi & Horton*, 169 USPQ 367 (CCPA 1971); emphasis as in original.

B. "How to Use" Requirement

The Action appears to have overlooked the practical requirements of utility and enablement. Any practical usefulness is sufficient to satisfy the utility requirement of § 101 and the "how to use" requirement of § 112, first paragraph. *Cross v. Iizuka*, 224 USPQ 739, 748 (Fed. Cir. 1985); *In re Brana*, 34 USPQ 2d 1436 (Fed. Cir. 1995).[1]

The claimed DNA segments have numerous practical uses outside recombinant expression, such as their use in various hybridization and cloning embodiments. Where the DNA segments are used in recombinant expression, there is absolutely no requirement that the expressed protein or polypeptide be enzymatically active. The requirements are only that a skilled artisan be able to make and use the DNA segments without undue experimentation (§ 112, first paragraph) and that the product have some practical utility (§ 101).

The Action does not question the ability of an artisan to practice recombinant expression techniques, so the § 112 requirement is met. As P-TEFb subunits may be used in various

[1] Although *Cross v. Iizuka* is often cited for the standard of practical utility under 35 U.S.C. § 101, the Federal Circuit also held the "how to use" requirement of 35 U.S.C. § 112, first paragraph to supported by the same level of practical (*i.e.*, *in vitro*) evidence. 224 USPQ at 748-749. This correlation between § 101 and § 112, first paragraph was stressed in the later case of *In re Brana*. In particular, see 34 USPQ 2d at 1439 and footnotes 9 and 12.

embodiments that do not require enzymatic activity, the § 101/§ 112 requirements are also met. In fact, the specification sets forth various uses for P-TEFb subunits without enzymatic activity, including as controls in activity studies; to bind and purify the counterpart subunit; to bind and purify interacting viral proteins, such as HIV Tat; and to identify potential inhibitors of viral interactions. It is even directly stated that "inactive products have utility in certain embodiments, such as, *e.g.*, in antibody generation" (specification at page 99, lines 2-3).

C. Testing for Functional Proteins

Where functional proteins are desired, the specification provides the requisite guidance on active P-TEFb subunits. In structural terms, it is explained that the cyclin-dependent kinase (CDK) includes the "PITALRE" sequence (specification at pages 12, 173) and has all the conserved subdomains found in CDKs, such as a conserved threonine residue at the T-loop in the catalytic subunit (specification at page 169, second paragraph). For the large, cyclin subunit, the specification teaches that this subunit has a conserved, canonical cyclin box domain (specification at pages 169, 170), which is located between amino acids 1 and 252-253 in the human cyclins (specification at page 178).

More importantly, the specification includes significant details regarding the functions of the subunits and provides numerous assays (phosphorylation, transcription elongation and viral transcription elongation) by which potential P-TEFb subunits can be tested and compared to subunits having the native sequences. Any experimentation required would thus be confined to very routine matters of protein production and functional assays, each of which are described at length in the specification.

Should any experimentation be necessary, it would certainly not rise to the level of "undue experimentation". In assessing the question of whether undue experimentation would be required, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (C.C.P.A. 1976). The need for some experimentation does not render the claimed invention unpatentable under 35 U.S.C. § 112, first paragraph. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra.*

The issue in this case is similar to that decided by the Federal Circuit in *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (although any experimentation in the present case should be less than in *Wands*). In *Wands*, the P.T.O. took the position that the applicant failed to demonstrate that the disclosed biological processes of immunization and antibody selection could reproducibly result in a useful biological product (antibodies from hybridomas) within the scope of the claims. In its decision overturning the P.T.O.'s rejection, the Federal Circuit found that Wands' demonstration of success in four out of nine cell lines screened was sufficient to support a conclusion of enablement. The court emphasized that the need for some experimentation requiring, *e.g.*, production of the biological material followed by routine screening, was not a basis for a finding of non-enablement, stating:

> "Disclosure in application for the immunoassay method patent does not fail to meet enablement requirement of 35 USC 112 by requiring 'undue experimentation,' even though production of monoclonal antibodies necessary to practice invention first requires production and screening of numerous antibody producing cells or 'hybridomas,' since practitioners of art are prepared to screen

negative hybridomas in order to find those that produce desired antibodies, since in monoclonal antibody art one 'experiment' is not simply screening of one hybridoma but rather is entire attempt to make desired antibody, and since record indicates that amount of effort needed to obtain desired antibodies is not excessive, in view of Applicants' success in each attempt to produce antibody that satisfied all claim limitations."

8 U.S.P.Q.2d at 1400.

The parallels between *Wands* and the present case are striking. Practice of the presently claimed invention does not require undue experimentation, even though the production of various P-TEFb subunits "may" require screening to confirm activity. Practitioners in the art routinely conduct functional screening assays, and one experiment would not be simply testing one P-TEFb variant, but rather an entire process of P-TEFb production.

D. Breadth of Working Examples

The Action at the bottom of page 4 states that "no working examples of an enzymatically active large subunit of P-TEFb comprising only 7 contiguous amino acids of SEQ ID NOs: 4, 45, 47 or 50 are provided besides SEQ ID NOs: 4, 45, 47 or 50". This circular argument entirely misses the point. The details in the specification would be better stated as: "after providing SEQ ID NO:4, the specification provides 3 further working examples of enzymatically active P-TEFb large subunits, namely those of SEQ ID NO:45, 47 and 50".

This invention first provides the *Drosophila* large subunit sequence of SEQ ID NO:4, and then the three human large subunit sequences of SEQ ID NO:45, 47 and 50. The specification teaches that two of the human proteins are very similar (HBL1-1 and HBL1-2), but that the third (HBL3) shares only an identity of 54% and a relative similarity of 70%, although conservation within the cyclin box is higher (specification at page 178, second full paragraph). When

compared to the *Drosophila* large subunit, the human proteins are only about 42% (HBL1-1 and HBL1-2) and 34% (HBL3) identical, although conservation within the cyclin box is again higher (specification at page 178, third full paragraph).

It is therefore important to note that each of the human sequences can substitute for the *Drosophila* large subunit in functional assays. The specification teaches that "the proteins encoded by HBL1-1, HBL1-2 and HBL3 can functionally act as the P-TEFb large subunit in *Drosophila* and likely act in a homologous manner in humans" (specification at page 180, first paragraph). This was confirmed by studies showing that recombinant human P-TEFb small and large subunits reconstitute Tat transactivation (specification bridging pages 180-181; FIG. 6); and by the volume of data presented in Examples 6 and 7.

As the breadth of the working examples is entirely commensurate with the scope of the claims, the § 112 rejection should be withdrawn even as it applies to DNA segments encoding functional proteins. There is simply no reason to doubt the objective truth that specification complies with the enablement requirements of § 112, first paragraph. *In re Marzocchi & Horton, supra.*

The § 112, first paragraph rejection as a whole is therefore overcome and should be withdrawn.

VI. Formalities

Please note that Applicant's representative, Shelley Fussey, has changed law firms and now practices at Williams, Morgan & Amerson in Houston. A new Power of Attorney is enclosed, and the new address and telephone number for Dr. Fussey are also listed at the end of this document.

VII. Conclusion

This is a complete response to the referenced Official Action. In conclusion, Applicant submits that, in light of the foregoing remarks, the present case is in condition for allowance and such favorable action is respectfully requested. Should Examiner Tung have any questions or comments, or believe that certain amendments of the claims might serve to even further improve their clarity, a telephone call to the undersigned Applicant's representative is earnestly solicited.

Respectfully submitted,

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